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Palladium-Catalyzed Selective Dehydrogenative Cross-Couplings of Heteroarenes**

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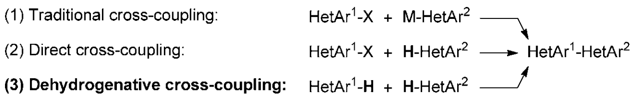
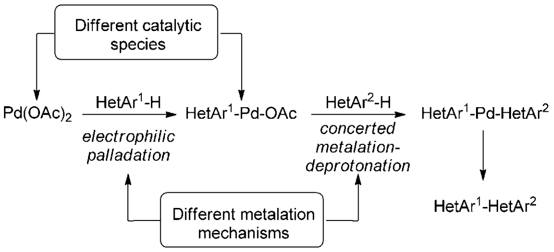
biaryls · C–H bond activation · heterocycles · oxidative cross-coupling · palladium

Heteroaromatic biaryls are important structural motifs in organic molecules, from natural products and bioactive compounds to advanced materials and liquid crystals. For this reason, the development of new methods for the synthesis of biheteroaryl scaffolds remains an ongoing challenge for organic chemists.[1] The traditional approach has involved the palladium-catalyzed cross-coupling between two previously activated substrates, a heteroaryl halide and an organometallic species (1). Over the last decades, the activation of C–H bonds has emerged as an active field in organometallic catalysis, which allows for superior step- and atom-economic transformations (2).[2] This novel strategy is even more appealing for heteroaromatic substrates as their organometallic derivatives are often troublesome to prepare and/or unstable.[3] Recently, the groups led by Hu and You,[4] Zhang and Li,[5] Yamaguchi and Itami,[6] and Ofial[7] pushed this concept one step further, designing selective palladium-catalyzed dehydrogenative cross-couplings of two heteroarenes (3) which obviate the need for any preactivation of the substrates.[8]

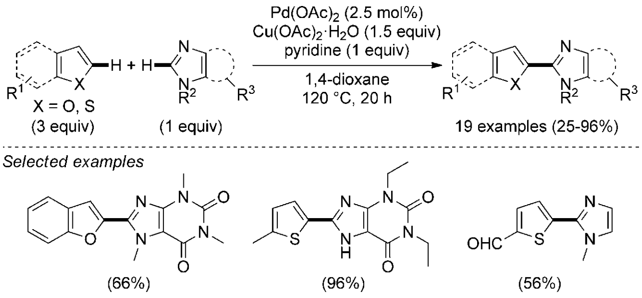


While improving synthetic efficiency, this new strategy, as it invokes the activation of two different C–H bonds, raises considerable challenges in terms of both chemo- and regioselectivity. As pointed out by the authors,[4a,7] differences between the two consecutive metalation steps are likely the key to success (Scheme 1). It may be assumed that the first metalation step, an electrophilic palladation,[9] modifies the properties of the catalytic species, thereby inducing selectivity for the second step, which may occur by means of a concerted metalation–deprotonation mechanism.[10] Such a scenario has already been put forward by Fagnou et al. when they described the dehydrogenative cross-coupling between indoles and unactivated benzene derivatives.[11]



Scheme 1. Two different catalytic species facilitate two chemoselective and mechanistically distinct metalation steps.

In their first report, Hu, You et al. described the Pd(OAc)$_2$-catalyzed dehydrogenative cross-coupling between π-electron-rich five-membered heterocycles (furans and thiophenes, along with their benzannulated analogues) and various families of N-containing heterocycles.[4a] Azoles, benzazoles, and xanthines react efficiently, with low catalyst loading and an excess of $Cu(OAc)_2{\cdot}H_2O$ as the oxidant, affording the heterodimer, in moderate to high yields (Scheme 2). An impressive level of selectivity is achieved with only a moderate excess of the second coupling partner (3 equiv). DFT calculations suggest that the first metalation readily occurs at the 2-position of the electron-rich five-membered heterocycle. The intermediate heteroarylpalladi-



Scheme 2. Selective oxidative cross-couplings of (benzo)thiophenes and (benzo)furans with xanthines and (benz)azoles.[4a]

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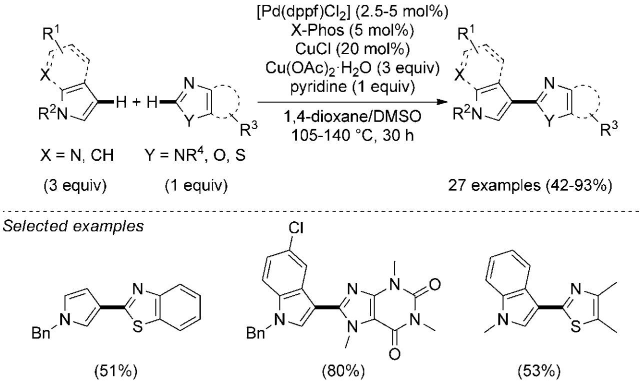
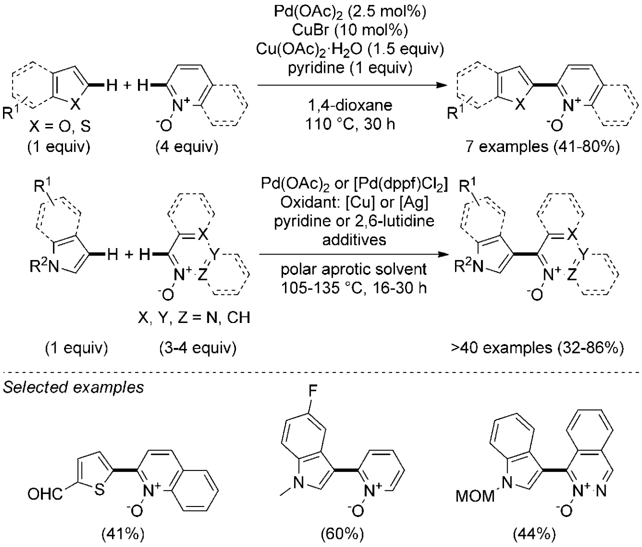
um(II) species then reacts preferentially with the other heterocycle, which bears a more acidic proton.

Indoles and pyrroles are other families of very interesting π-electron-rich heterocycles. However, their use in a similar transformation proved to be challenging because of their sensitivity to the oxidative conditions of the reaction. Very recently, You et al. extended their methodology by showing that indoles and pyrroles could successfully participate in the reaction, affording C3-heteroarylation products (Scheme 3).[4b] The use of X-Phos as the ligand and a Cu^{I} salt as the cocatalyst minimizes the oxidative degradation of these sensitive starting materials and increases the C3/C2 regioselectivity. Furthermore, DMSO as a cosolvent often has a very positive impact on the reaction outcome.



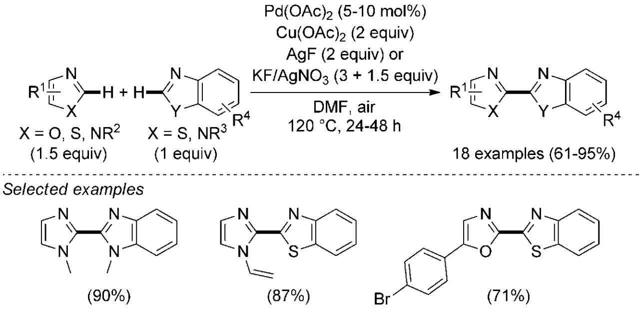
Scheme 3. Selective oxidative cross-couplings of indoles and pyrroles with xanthines and (benz)azoles.[4b]

Electron-poor azine *N*-oxides represent a second class of heterocycles that can be cross-coupled with electron-rich heteroarenes (Scheme 4). Hu, You et al. first implemented this strategy by designing a cross-coupling with furans and (benzo)thiophenes.[4a] This time, an excess of the *N*-oxide with CuBr as the cocatalyst was found useful in increasing the efficiency of the cross-coupling, thereby preventing homodimerization of the other reactant. Based on literature precedent, the second C–H bond cleavage most likely also occurs through concerted metalation–deprotonation.[12] Thereafter, several further contributions describing the cross-coupling of indoles and pyrroles with a large variety of azine *N*-oxides were reported by the groups of Zhang and Li,[5] Yamaguchi and Itami,[6] and You.[4b]



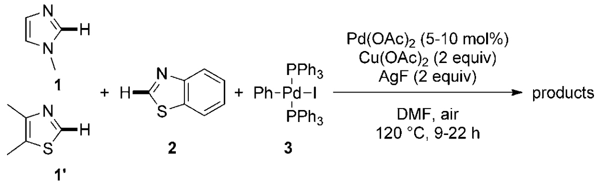
Scheme 4. Selective oxidative cross-couplings of (benzo)thiophenes and furans with azine *N*-oxides.[4–6]

Besides this, the group of Ofial independently developed an impressively selective dehydrogenative cross-coupling of azoles with benzazoles (Scheme 5).[7] This method represents an efficient access to the 2,2′-linkage between azoles, a surprisingly rare and unexplored motif.[13] A set of mechanistic experiments helped to provide insight into the origin of this selectivity (Table 1). At first, the authors showed that azole **1**, when placed alone under the reaction conditions, is rapidly consumed (entry 1), whereas benzazole **2** remains mostly unchanged (entry 2). Interestingly, the latter heterocycle can be arylated using the preformed arylpalladium(II) species **3** (entry 3) and the rate of arylation seems to be comparable to the rate of biheteroaryl formation (entry 4). Moreover, the presence of Ag^{+} ions was mandatory for a highly selective cross-coupling (entries 5 and 6). These



Scheme 5. Selective oxidative cross-couplings of azoles with benzazoles.[7]

Table 1: Mechanistic studies on the selective oxidative cross-couplings of azoles with benzazoles.[7]



Entry	Substrates	Results
1	only **1**	high conversion (> 90 %)
2	only **2**	low conversion (< 10 %)
3	**2** + **3**	phenylation of **2** (74 %)
4	**1** + **2** + **3**	biheteroaryl (65 %) + phenylation of **2** (33 %)
5	**1′** + **2**	biheteroaryl (92 %) + dimerization of **1′** (< 5 %)
6[a]	**1′** + **2**	biheteroaryl (41 %) + dimerization of **1′** (43 %) + dimerization of **2** (15 %)

[a] Without Ag^{+}.

observations point towards a fast initial palladation of the more electron-rich azole to afford a heteroarylpalladium(II) intermediate, which can promote a second C–H bond cleavage selectively with the benzazole. Even though this second metalation may occur with concomitant deprotonation from the acetate as an internal base, it should be pointed out that the pK_a values of the C2–H bonds of the azoles are not sufficient to explain the striking selectivity.[7,14] Instead, complexations of the different cations present in the reaction mixture with the heteratoms of the substrates might play an important role.

In conclusion, the groups of Hu and You,[4] Zhang and Li,[5] Yamaguchi and Itami,[6] and Ofial[7] have described the first highly selective dehydrogenative cross-couplings of heterocycles to afford valuable biheteroaryls. Further development in this field will provide more insight into the mechanism and expand the scope of these transformations, maybe even to the ubiquitous 2,4′-bisazole linkage.[13] Think differently about biheteroaryl formation!

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